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PRINCIPAL INVESTIGATOR: Charles S. Cox, Jr, M.D.

CONTRACTING ORGANIZATION: The University of Texas Health Sciences Center at Houston
Houston, TX 77030-5400

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Charles S. Cox, Jr, M.D.
E-Mail: Charles.S.Cox@uth.tmc.edu

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14. ABSTRACT Traumatic brain injury (TBI) contributes to 50% of all trauma deaths. The mortality rate for adults following severe TBI (Glasgow Coma Scale < 9) is estimated to be 33%. There is currently no therapy to reverse the primary injury associated with TBI. There has been a growing body of literature supporting the use of various progenitor cell types to treat acute neurological injuries such as TBI. Our primary hypothesis is that bone marrow mononuclear cell (BMMNC) autologous transplantation after TBI is safe. Our secondary hypothesis is that functional outcomes measures will improve after BMMNC infusion, (3) BMMNC infusion will reduce BBB permeability, and (4) BMMNC is neuroprotective and preserves grey and white matter volumes after TBI. This is a dose-escalation study consisting of 4 cohorts including a control group (5 subjects/cohort). Subjects in the control group will not undergo the bone marrow harvest procedure and will receive only the standard of care for TBI patients. All subjects (including those in the control group), will be followed for safety, have plasma & CSF (if available) collected for neuroinflammatory markers. The 1 & 6 month follow-up visits include physical and neurological exams, neuropsych. & functional outcomes tests, blood sample for routine labs and neuro-inflammatory markers, & a DTMRI. As of 31 May 2014, 20 subjects have been enrolled (5 control, 15 treatment). All subjects had in-patient plasma & CSF (when available) collected for neuroinflammatory markers. Seventeen subjects have completed the study including one control group subject who was lost to follow-up after discharge. The three remaining subjects have completed the 1-month visit and have 6-month end of study visits scheduled. Per protocol, the medical monitor has reviewed all subject records and no serious adverse events related to the BMMNC infusion have been reported. The DSMB met on 10 January 2014 & reviewed safety data on the 17 subjects enrolled in the study at that time. No subject safety issues were identified and the DSMB recommended the study continue as is with no protocol modifications. Our most recent clinical monitor visit was 11 March 2014.

15. SUBJECT TERMS
Traumatic Brain Injury, Bone Marrow Mononuclear Cells

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TREATMENT OF ADULT SEVERE TRAUMATIC BRAIN INJURY USING AUTOLOGOUS BONE MARROW MONONUCLEAR CELLS

Annual Progress Report (01-June-2013 to 31-May-2014)

Introduction:

Traumatic brain injury (TBI) contributes to 50% of all trauma deaths. The mortality rate for adults following severe TBI (Glasgow Coma Scale < 9) is estimated to be 33%. There is currently no therapy to reverse the primary injury associated with TBI. Over the past 10 years there has been a growing body of literature supporting the use of various progenitor cell types to treat acute neurological injuries such as TBI and stroke. Neural stem cells (adult and embryonic), mesenchymal stromal and multipotent adult progenitor cells, and bone marrow mononuclear cells (from which MSC and MAPCs are derived) have all shown efficacy in pre-clinical models of TBI/stroke through various mechanisms; however, few groups believe that true neural replacement and integration are the putative mechanisms involved in the observed efficacy. More likely is that the progenitor cell populations are modifying the regional response to injury (inflammatory/reparative vs. regenerative), resulting in improved functional outcomes. Our primary hypothesis is that bone marrow mononuclear cell (BMMNC) harvest and autologous transplantation after TBI is safe. Our secondary hypotheses are that functional outcomes measures will improve after BMMNC infusion, BMMNC infusion will reduce BBB permeability, and lastly, BMMNC's are neuroprotective and preserve grey matter and white matter volume after TBI.

Progress Report:

Screening procedures for study eligibility were followed per protocol and research consent obtained from the legal authorized representative(s) [LAR] of patients meeting inclusion/exclusion criteria.

The dose-escalation design as described in the protocol was successfully implemented and consisted of 4 cohorts including a control group (5 subjects/cohort). Safety monitoring procedures during hospitalization were the same for all cohorts. The 1 and 6 month follow-up visits included a physical-neurological exam, neuropsychiatric and functional outcome tests, routine lab tests, a blood sample for neuroinflammatory markers, and a DTMRI. Cumulative enrollment data is displayed in figure 1 on the next page.

- Five subjects were enrolled in the control group and did not undergo bone marrow harvest/infusion. Four control subjects completed the 1 and 6 month follow-up visits. One control group subject was lost to follow-up after discharge. The subjects' vital status is known to be "living".
- Five subjects received the lowest dose target of $6X10^6$ mononuclear cells/kilogram body weight and all five have completed the 1 and 6 month follow-up visits.
- Five subjects received the middle dose target of $9x10^6$ mononuclear cells/kilogram body weight and all five have completed the 1 and 6 month follow-up visits.
- Five subjects received the high dose target of $12X10^6$ mononuclear cells/kilogram body weight and 2 of the subjects in this cohort have completed the 1 and 6 month study visits. The other 3 subjects have completed the 1 month follow-up visit and have the 6 month return visit scheduled.

Figure 1: Cumulative Enrollment

Subject #	Enrollment Date	Age (years)	Gender	Race	Status
1	3/28/2012	18	M	Asian	All Visits Completed.
2	4/11/2012	19	M	African-American	Lost to follow-up after discharge.
3	4/12/2012	51	M	White	All Visits Completed.
4	6/17/2012	52	F	White	All Visits Completed.
5	8/16/2012	41	M	White	All Visits Completed.
6	10/18/2012	33	M	African-American	All Visits Completed.
7	11/27/2012	20	M	White	All Visits Completed.
8	2/8/2013	17	F	White	All Visits Completed.
9	2/28/2013	37	M	White	All Visits Completed.
10	3/17/2013	19	M	White	All Visits Completed.
11	4/7/2013	44	M	White	All Visits Completed.
12	5/25/2013	22	M	White	All Visits Completed.
13	7/14/2013	28	F	White	All Visits Completed.
14	7/25/2013	33	M	White	All Visits Completed.
15	8/10/2013	28	M	White	All Visits Completed.
16	9/10/2013	23	M	White	All Visits Completed.
17	11/16/2013	34	F	White	All Visits Completed.
18	3/28/2014	43	F	White	Completed 1 month visit, 6 mo. visit scheduled Sept. 2014.
19	4/6/2014	36	M	African-American	Completed 1 month visit, 6 mo. visit scheduled Oct. 2014.
20	4/7/2014	36	M	Hispanic	Completed 1 month visit, 6 mo. visit scheduled Oct. 2014.

Preliminary Analysis of Primary Safety Outcomes

All subjects were managed according to the established guidelines for the care of adults with severe traumatic brain injury. All subjects received an intracranial pressure monitor /ventriculostomy for ICP measurement.

1. Hemodynamic Instability during BMMNC Harvest:

There were no significant hemodynamic changes during the bone marrow harvest, nor was there a significant drop in the hemoglobin/hematocrit after the procedure.

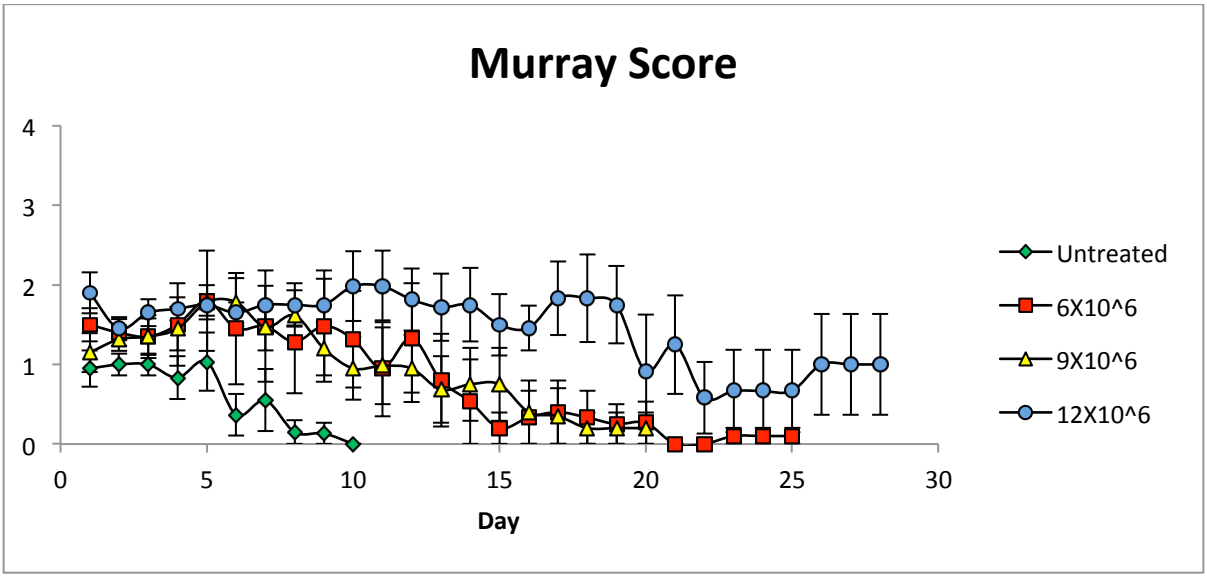
2. BMMNC Harvest Complications:

The 15 subjects undergoing BMMNC harvest were closely monitored for indications of harvest puncture site infection, hemorrhage, or other procedure related complications. No BMMNC harvest related complications occurred.

3. Pulmonary Complications:

All subjects were monitored for lung injury using established guidelines for ICU care of patients with TBI. Pulmonary function was measured using the Murray score, which is an accepted composite of the following variables: PaO2:FIO2 ratio, positive end-expiratory pressure, respiratory compliance, degree of chest radiograph infiltrate (Murray, 1988). The final score is an average of the aggregate summed components. For perspective, a Murray score of 3 indicates profound respiratory failure and has been used as the primary entry criteria for extracorporeal life support. None of the subjects developed ARDS or significant impairment in oxygenation/ventilation within the first 48 hours of stem cell infusion that would have triggered protocol stopping rules and DSMB review.

Figure 2: Murray Scores



4. Hepatic Injury:

The hepatic transaminases (AST and ALT) were measured daily as an index of hepatic injury/toxicity. Mild elevated liver enzymes, (NCI CTCAE V4 Grade 2 or less) were observed in all cohort groups including the controls and attributed to routine seizure prophylaxis, (fosphenytoin and/or phenytoin). There was no evidence of clinically significant hepatocyte injury as the liver enzymes did not significantly increase.

5. Neurological Complications:

All subjects were monitored according to the standard TBI ICU policies. Standard of care data including GCS, ICP, CPP, pupillary size/reactivity, motor/sensory evaluation of extremities, and seizure activity were closely monitored. A complete neurological exam was performed daily. There were no Grade 4-5 CNS cerebrovascular ischemia events or Grade 4-5 seizure events as defined in the NCI CTCAE v4.0, or other neurological complications occurring within 12 hours of BMPC re-infusion.

6. Summary of Preliminary Safety Data

Safety data was collected for all 20 subjects during hospitalization. Adverse events were reported for all cohort groups, as expected for patients with severe TBI. No adverse events were associated with, or temporally related to the stem cell infusion. Patient safety reports were provided to the study Medical Safety Monitor (MSM) immediately after post-infusion day

14 and MSM approval was obtained before enrollment of patients in the next dose escalation cohort. Safety information for the first 17 subjects was reviewed at the last DSMB meeting (Jan. 2014). The DSMB approved continuation of the study with no protocol changes.

Figure 3: Control Group

Subject	Adverse Event	Admit Date	Infusion Date	AE/SAE Severity Grade	AE/SAE Start Date	Relationship to Stem Cell Intervention	Adverse Event Status at Last Contact
1	Elevated Liver Enzymes	3/28/2012	NA-Control	1	3/29/2012	NA	Resolved
	Subsegmental Pulmonary Atelectasis			1	4/1/2012	NA	Resolved
	Anemia Associated with Blood Loss from Trauma Injuries			2	4/1/2012	NA	Resolved
	Tachycardia			1	4/3/2012	NA	Resolved
	Fever			2	4/4/2012	NA	Resolved
	Respiratory Infection			1	4/5/2012	NA	Resolved
	Agitated Behavior Reported			1	4/8/2013	NA	Resolved
2	Anemia Associated with Blood Loss from Trauma Injuries	4/11/2012	NA-Control	1	4/12/2012	NA	Resolved
	Elevated INR			1	4/12/2012	NA	Resolved
3	Bradycardia	4/11/2012	NA-Control	1	4/12/2012	NA	Resolved
	Anemia Associated with Blood Loss from Trauma Injuries			2	4/13/2012	NA	Resolved
	Emotional Instability Reported at 6 Mo. Follow-up Visit			1	10/10/2012	NA	Ongoing
4	Tachycardia	6/16/2012	NA-Control	1	6/17/2012	NA	Resolved
	Anemia Associated with Blood Loss from Trauma Injuries			1	6/19/2012	NA	Resolved
	Leukocytes in Urine			1	6/26/2012	NA	Resolved
	Elevated Liver Enzymes			1	6/28/2012	NA	Resolved
5	Tachycardia	8/16/2012	NA-Control	1	8/23/2012	NA	Resolved
	Anemia Associated with Blood Loss from Trauma Injuries			1	8/23/2012	NA	Resolved
	Fever			1	8/23/2012	NA	Resolved
	Hyperlipidemia			1	9/5/2012	NA	Resolved
	Elevated Liver Enzymes			1	2/13/2013	NA	Ongoing

Figure 4: Low Dose Cohort ($6x10^6$ mononuclear cells/kilogram body weight)

Subject	Adverse Event	Admit Date	Infusion Date	AE/SAE Severity Grade	AE/SAE Start Date	Relationship to Stem Cell Intervention	Adverse Event Status at Last Contact
6	Pneumonia	10/18/2012	10/19/2012	3	10/21/2012	Unlikely	Recovering
	Fever			2	10/21/2012	Unrelated	Resolved
	Elevated WBC Count			2	10/21/2012	Unrelated	Resolved
	Anemia Associated with Blood Loss from Trauma Injuries			2	10/21/2012	Unrelated	Resolved
	Elevated Liver Enzymes			2	10/26/2012	Unlikely	Resolved
	Tachycardia			1	10/28/2012	Unlikely	Resolved
	Long-Term Memory Loss Reported at 6 Mo. Follow-up Visit			1	4/29/2013	Unrelated	Ongoing
7	Elevated Liver Enzymes	11/26/2012	11/27/2012	1	11/29/2012	Unlikely	Resolved
8	Anemia Associated with Blood Loss from Trauma Injuries	2/7/2013	2/8/2013	1	2/8/2013	Unlikely	Resolved
	Fever			1	2/9/2013	Unlikely	Resolved
	Atelectasis			2	2/10/2013	Unrelated	Resolved
9	Anemia Associated with Blood Loss from Trauma Injuries	2/28/2013	3/1/2013	3	3/1/2013	Unrelated	Resolved
	Decreased ICP Pressure			2	3/1/2013	Unlikely	Resolved
	Pneumonia			1	3/6/2013	Unlikely	Resolved
	Pulmonary Venous Hypertension noted on Chest X-Ray			1	3/9/2013	Unlikely	Resolved
	Elevated WBC Count			1	3/11/2013	Unlikely	Resolved
	Elevated Platelet Count			1	3/12/2013	Unlikely	Resolved
10	Intermittent Intracranial Hypertension	3/17/2013	3/18/2013	3	3/17/2013	Unrelated	Resolved
	Anemia Associated with Blood Loss from Trauma Injuries			1	3/17/2013	Unrelated	Resolved
	Pneumonia (Aspiration Pneumonitis)			4	3/20/2013	Unlikely	Resolved
	Right Basilar Pneumothorax noted on Chest X-Ray			2	3/20/2013	Unrelated	Resolved
	Respiratory Failure (Submitted to DSMB/HRPO 3/25/2013)			4	3/20/2013	Unrelated	Resolved
	Hypoxemia			4	3/20/2013	Unrelated	Resolved

Figure 5: Middle Dose Cohort ($9x10^6$ mononuclear cells/kilogram body weight)

Subject	Adverse Event	Admit Date	Infusion Date	AE/SAE Severity Grade	AE/SAE Start Date	Relationship to Stem Cell Intervention	Adverse Event Status at Last Contact
11	Anemia Associated with Blood Loss from Trauma Injuries	4/7/2013	4/9/2013	1	4/9/2013	Unrelated	Resolved
	Tachycardia			1	4/12/2013	Unrelated	Resolved
	Leukocytosis			1	4/16/2013	Unlikely	Resolved
	Pneumonia			2	4/17/2013	Unlikely	Resolved
	Diffuse Encephelpathy on EEG			2	4/17/2013	Unrelated	Resolved
	Blurred Vision Reported at Follow-up Visit			1	5/15/2013	Unrelated	Ongoing
	Short Tem Memory Loss Reported at Follow-up Visit			1	5/15/2013	Unrelated	Ongoing
12	Fever	5/25/2013	5/26/2013	1	5/27/2013	Unlikely	Resolved
	Tachycardia			1	5/29/2013	Unlikely	Resolved
	Fall			2	6/7/2013	Unrelated	Resolved
13	Fever	7/14/2013	7/15/2013	2	7/15/2013	Unrelated	Resolved
	Bradycardia			3	7/15/2013	Unrelated	Resolved
	Hypothermia			2	7/15/2013	Unrelated	Resolved
	Elevated ICP			4	7/15/2013	Unrelated	Resolved
	Anemia Associated with Blood Loss from Trauma Injuries			3	7/15/2013	Unrelated	Resolved
	Leukocytosis			2	7/15/2013	Unrelated	Resolved
	Elevated Liver Enzymes			2	7/19/2013	Unrelated	Resolved
	UTI			2	7/20/2013	Unrelated	Resolved
	Pneumonia			3	7/28/2013	Unrelated	Resolved
14	Respiratory Distress/Hypoxia	7/25/2013	7/26/2013	3	7/26/2013	Unrelated	Resolved
	Anemia Associated with Blood Loss from Trauma Injuries			2	7/27/2013	Unrelated	Resolved
	Leukocytosis			3	8/1/2013	Unrelated	Resolved
15	Anemia Associated with Blood Loss from Trauma Injuries	8/10/2013	8/11/2013	3	8/11/2013	Unrelated	Resolved
	Tachycardia			2	8/12/2013	Unrelated	Resolved
	Elevated INR			3	8/14/2013	Unrelated	Resolved
	Hypertension			2	8/16/2013	Unrelated	Resolved
	Elevated Liver Enzymes			2	8/17/2013	Unrelated	Resolved
	Pneumonia			3	8/19/2013	Unrelated	Resolved

Figure 6: High Dose Cohort ($12x10^6$ mononuclear cells/kilogram body weight)

Subject	Adverse Event	Admit Date	Infusion Date	AE/SAE Severity Grade	AE/SAE Start Date	Relationship to Stem Cell Intervention	Adverse Event Status at Last Contact
16	Desaturation / Hypoxia	9/9/2013	9/10/2013	3	9/10/2013	Unrelated	Resolved
	Tachycardia			2	9/10/2013	Unrelated	Resolved
	Increased Intracranial Pressure			4	9/13/2013	Unrelated	Resolved
	Hypertension			3	9/13/2013	Unrelated	Resolved
	Atelectasis			2	9/16/2013	Unrelated	Resolved
	Pneumothorax			2	9/18/2013	Unrelated	Resolved
	Pulmonary Embolism			4	9/21/2013	Unrelated	Resolved
17	Increased Intracranial Pressure	11/15/2013	11/16/2013	4	11/16/2013	Unrelated	Resolved
	Stroke			3	11/17/2013	Unrelated	Recovering
	Fevers			1	11/20/2013	Unrelated	Resolved
	DVT			2	12/4/2013	Unrelated	Recovering
18	Leukocytosis	3/27/2014	3/28/2014	2	4/3/2014	Unrelated	Resolved
	Peritracheal Erythema, Localized Edema			2	4/7/2014	Unrelated	Resolved
19	Depressed Level of Consciousness	4/6/2014	4/7/2014	5	4/8/2014	Unrelated	Recovering
	Cerebral Edema			4	4/8/2014	Unrelated	Resolved
	Coagulopathy			4	4/9/2014	Unrelated	Resolved
	Subarachnoid Hemmorhage			3	4/9/2014	Unrelated	Resolved
	Acute Renal Failure			3	4/9/2014	Unrelated	Resolved
	Multiorgan Failure			4	4/9/2014	Unrelated	Resolved
	Brain Herniation			4	4/9/2014	Unrelated	Recovering
20	Contusion/Atelectasis of Left Basilar Lobe	4/5/2014	4/7/2015	3	4/5/2014	Unrelated	Resolved
	Stroke			2	4/13/2014	Unrelated	Recovering
	UTI			3	4/14/2014	Unrelated	Resolved
	Pneumonia			3	4/14/2014	Unrelated	Resolved

Late Outcome Efficacy Measures

1. Correlation of Intracranial Pressure to Neuroinflammation & Neuroinflammatory Markers:

An analysis of intracranial pressure to plasma & CSF neuroinflammatory biomarkers is underway.

2. Neuroinflammation:

An analysis of plasma and CSF is underway.

3. Neuropsychological and Functional Outcomes Measures:

One month neurobehavioral outcome data was obtained on 19 out of 20 subjects enrolled in the study. One control group subject was lost to follow-up after discharge. Six month neurobehavioral outcome data was obtained on 16 subjects and the remaining 3 subjects will complete the 6 month evaluations in Sept./Oct. of 2014. Caregivers were interviewed regarding subjects' level of global functioning. Figures 7 shows preliminary analysis of global outcome scores by group and time of assessment. GOS-E scores were available for only two subjects in the high dose group at the time this report was prepared. Because Chi square analysis is unreliable when there are less than 5 observations in a group; the 2 subjects in the high dose group were not included in the 1 to 6 month GOS-E Score changes depicted in figure 8.

Figure 7:

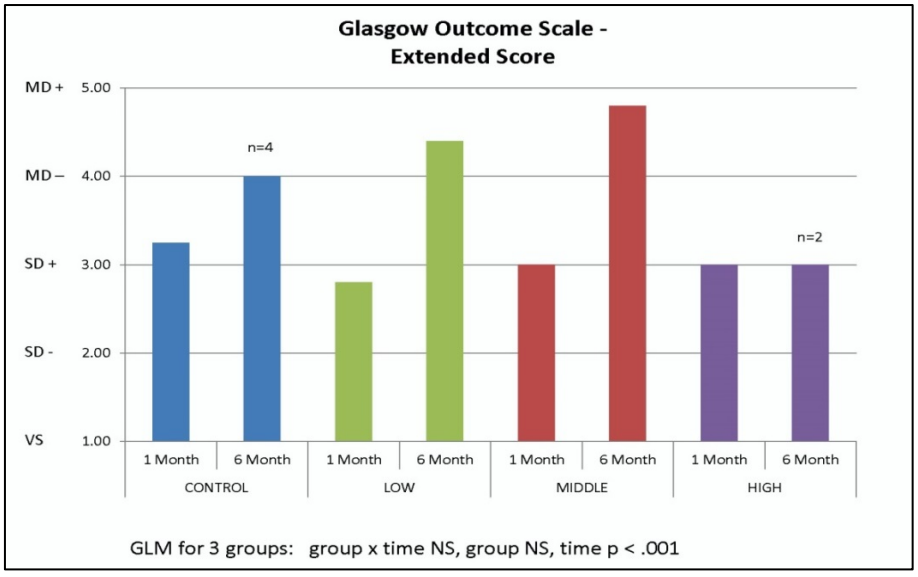


Figure 8:

Change in GOS-E Scores from 1 to 6 Months

	CONTROL	LOW	MID	HIGH
No change	3	1	1	2
+1 category	1	1	2	
+2		2		
+3 or more		1	2	

Chi square for GOS change: control vs combined low/middle dose: p = .095
Controls: 1 of 4 improved=25% Treatment: 8 of 10 =80%

Figure 9:

Number of Patients in GOS-E Outcome Categories

	Control		Low Dose		Middle Dose		Low + Mid Dose		High Dose	
GOS-E Category (n)	1m	6m	1m	6m	1m	6m	1m	6m		
Vegetative			1				**1**	**0**		
Severe Disability										
Lower	**3**	**2**	4	2	5	1	**9**	**3**	*5*	*2*
Upper	**1**	**1**				2	**0**	**2**		
Moderate Disability										
Lower				2			**0**	**2**		
Upper		**1**		1		1	**0**	**2**		
Good Recovery										
Lower						1	**0**	**1**		
Upper										

4. Structural Correlates to Outcome:

DTMRI images at one month post head injury were obtained on 19 subjects. One control subject was lost to follow-up after discharge. Six month DTMRI images have been

completed for 16 subjects. Three subjects will complete the 6 month visit with DTMRI during Sept.-Oct. of 2014. Analysis of DTMRI images is underway.

Key Research Accomplishments:

CY11 Goals- Regulatory Approval of Protocol

☑ FDA IND Approved APR 2011, IRB Approved OCT 2011, and HRPO Approved DEC 2011.

CY12 Goals - Study Initiation & Enrollment

☑ Enrollment of 1st Cohort (Control) Group Started MAR 2012, Completed AUG 2012.
☑ Enrollment of 2nd Cohort ($6x10^6$ BMMNC/kg) Started OCT 2012.

CY13 Goal - Safety Monitoring & Dose Escalation

☑ Enrollment of 2nd Cohort ($6x10^6$ BMMNC/kg) Completed MAR 2013.
☑ Enrollment of 3rd Cohort ($9x10^6$ BMMNC/kg) Group Started APR 2013, Completed AUG 2013.
☑ DSMB Review of Safety Data JUN 2013. Recommendation to continue study with no changes.
☑ Enrollment of 4rd Cohort ($12x10^6$ BMMNC/kg) Group Started SEP 2013.

CY14 Goal – Completion of Enrollment & Data Analysis

☑ DSMB Review of Safety Data JAN 2014. Recommendation to continue study with no changes.
☑ Enrollment of 4rd Cohort ($12x10^6$ BMMNC/kg) Completed APR 2014.
☑ Data Analysis is Underway.

Comments/Challenges/Issues/Concerns:

A request is pending to extend the study to 30 APR 2015 allowing enrollment of additional control subjects for comparison to the treatment group.

Reportable Outcomes/Conclusion: This annual report contains preliminary data and analysis is ongoing.

References: None

Appendices: None